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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/613,887	HOGAN, KIRK	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *January 5, 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *74-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/04; 4/01; 1/00*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed January 5, 2004. Currently, claims 74-105 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. With respect to Applicant's request to provide a copy of the 1449 filed on 10/11/00 and 4/25/01, copies have been included with the instant action. It is noted that these 1449's had been initialed and appear to have been mailed with the Final rejection dated 6/25/01.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of applicant's arguments and the amendments to the claims.

4. The rejection of Bidwell has been withdrawn in view of the amendments to the claims. The claims require detecting two or more nucleic acid markers in two or more genes known to be associated with two or more perioperative phenotypes. Bidwell teaches detecting two or more makers in two or more genes, however fails to specifically teach that the markers are associated with two or more perioperative phenotypes. The alleotyping would be postoperative phenotypes, as determination of grafts being rejected or other complications following surgery. Therefore, Bidwell does not meet all of the limitations of the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 74-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol 88, No. 10, page 3698-3703, 1996) and further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999).

Miller teaches screening a patient preoperatively to determine a risk for complications during a surgical procedure. Miller teaches that patients meets with the surgeon to prepare for surgery. Miller teaches that the surgeon often informs the patient of the anesthetic preoperative requirements and presents the patient with a letter. A sample letter is provided which illustrates the date of the surgery with the time, and instructions that "it is also important that your blood tests, urinalysis, and any other tests ordered by your doctor be completed two days before you are scheduled for surgery so that they can be reviewed by your anesthesiologist prior to surgery". Miller therefore teaches the importance of a blood test prior to surgery to identify any abnormalities.

Miller does not specifically teach analyzing the blood taken from the patient within two days prior to surgery for "two or more known genetic variations associated with two or more conditions".

However, Quane et al (herein referred to as Quane) teaches the detection of novel common mutations in ryanodine receptor gene (RYR1) in malignant hyperthermia (MH). Malignant hyperthermia (MH) is triggered in susceptible people by all commonly used inhalation anesthetics. Quane has identified Gly341Arg mutation which accounts for approximately 10% of Caucasian MHS cases (abstract). Quane specifically teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided. Quane also teaches that Arg615Cys is a substitution found in 3-5% of human MH families investigated (page 472, col. 1); Arg163Cys is a substitution found in 2-3% of MHS cases. Furthermore, three other rare mutations have been reported in the RYR1 gene which are in three isolated MHS and/or CCD cases. Quane teaches that patients which have not been indicated as MH normal should always be considered MHS clinically to avoid any possibility of the individual reacting to a triggering agent during anesthesia. Misdiagnosis of MHS individual as MHN can be lethal if such a patient is exposed to triggering agents (page 474, col. 1). Quane teaches that the mutation reported satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means (page 474, col. 1). Quane analyzes genomic DNA from peripheral blood for the presence of the mutations (page 474, col 2).

Acta Anaesthesiologica Scandinavin (referred to as AAS) teaches that certain variants have a dramatic degree of resistance to the drug, succinylcholine (SC), because they destroy it so rapidly. AAS teaches that individuals show no regular metabolic disorder unless SC or mivacurium is given such that the condition is provoked. BchE mutations are dibucaine resistant, fluoride resistant or silent. SC and mivacurium are potentially toxic in people with BchE deficiency. AAS teaches that the principles of molecular biology tests and their application to BchE variants are well illustrates and anesthesiologists need to keep up to date about these applications. AAS also teaches that other hereditary conditions of special interest to anesthesiologists, such as malignant hyperthermia, may be diagnosed by similar methods in a few years (page 141).

La Du et al (herein referred to as La Du) teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine. Variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80).

Pharmacogenetics teaches polymorphisms of desbrisoquine hydroxylase (Cytochrome P4502D6). The structures of CYP2D gene clusters are provided. The poor metabolizers are depicted. Pharmacogenetics teaches that for drugs such as codeine and encainide it is the PM subjects who may experience therapeutic failure (page 317, col. 1). Codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. The discovery and identification of each of these conditions has saved some lives and may prevent future fatalities or morbidities.

Evans et al (herein referred to as Evans) teaches the drug-metabolizing enzyme debrisoquine hydroxylase (CYP2D6) is polymorphic. Evans teaches that "inherited differences in drug-metabolizing capacity are generally monogenic traits and their influence on the pharmacokinetices and pharmacologic effects of medications is determined by their importance for the activation or inactiviation of drug substrates (page 487, col. 2). Evens also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Evans illustrates in Figure 2, drug-metabolizing enzymes known to exhibit genetic polymorphisms with incontrovertible clinical consequences. Further, severe and potentially fatal hematopoietic toxicity that occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches that "many opioid analgesics are activated by CYP2D6 rendering the 2-10% of the population who are homozygous for nonfunctional CYP2D6 mutant alleles relatively resistant to opioid analgesic effects. Thus is it not surprising that there is remarkable interindividual variability in the adequacy of pain relief when uniform doses of codeine are widely prescribed" (page 489, col. 1). Evans teaches that individualizing drug dosages can improve clinical outcome (page 491, col. 1).

Poort et al (herein referred to as Poort) teaches an 20210 AG gentoype of the prothrombin gene which is a candidate for venous thrombosis in patients. It is well

known in the art that venous thromboembolism can occur without apparent cause, after surgical procedures or trauma. Poort also teaches that factor V Leiden is the most common hereditary risk factor for thrombosis. Poort teaches two genetic markers which are associated with thrombosis.

Moreover, Hoon et al. (herein referred to as Hoon) teaches the benefits of using multiple markers in detection assays. Hoon teaches using multiple markers provides increased sensitivity (abstract). Hoon teaches that marker combinations may be developed, which are particularly sensitive to the effect of therapeutic regimens on disease progress such that patients may be monitored (col. 4, lines 65-68). In a particular example, Hoon demonstrates that number of markers was studied and that using four markers was significantly better than a single marker alone (col. 21).

Additionally, Hacia teaches mutational analysis using oligonucleotide microarrays. Hacia teaches that arrays of 1,480 oligonucleotide probes were designed to detect 37 known mutations, probes were spotted on surfaces to detect mutations in HBB, and BRCA1. Hacia teaches that arrays of 135,000 probes were used to interrogate the entire 16.6kb human mitochondrial genome from ten samples (page 44, col. 1). Chips have also bee used for the simultaneous genotyping of 500 markers (page 45, col. 1). Hacia teaches that chips allow for unprecedented throughput in mutational analysis with a high degree of accuracy (page 46, col. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients prior to subjecting the patient to anesthetics, as taught by Miller, to determine whether they were at risk of MH,

a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, as taught by Quane, Acta Anaesthesiologica Scandinavica, La Du , Pharmacogenetics, Evans or Poort . Miller teaches that it is routine to sample patients blood to analyze the blood for abnormalities including hematocrit levels. Miller teaches that "the laboratory evaluation should be available for review by the anesthesiologist prior to or at the time he first sees the patients preoperatively so that any questions regarding the patient's status should be resolved then and if not resolved the surgery should be delayed" (page 1325). Quane provides three examples of common mutations within the RYR1 gene which are associated with MH and which trigger MH syndrome during anesthesia, and potentially death. Quane specifically states that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided" (page 471, col. 2). AAS teaches that SC and mivacurium are potentially toxic in people with BchE deficiency. La Du et al teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine and the variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80). Pharmacogenetics teaches that codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. Evens also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme

exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Additionally, Port teaches that factor V Leiden is the most common hereditary risk factor for thrombosis and two genetic markers which are associated with thrombosis.

Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within the RYR1, CYP2D6, Prothrombin, BCHE genes for the expected benefit of determining whether the patient possessed any mutations which were linked to the known condition of MH to avoid any fatal reaction to the anesthesia, for example. The ordinary artisan would have recognized that blood samples are routinely taken within two days prior to surgery and therefore to minimize inconvenience to the patient, the blood sample taken would also be an ideal sample for testing the patient for genetic abnormalities within RYR1. The ordinary artisan would have clearly recognized the benefit of testing an individual prior to surgery and subjection to the anesthesia for known genetic markers associated with a condition which was triggered by anesthetics.

Moreover, given the teachings of Hoon and Hacia that sampling multiple markers provides increase sensitivity, the ordinary artisan would also be motivated to have sampled additional markers which are associated with complications in surgery. Therefore, the skilled artisan would have additionally analyzed a patient for a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, as taught by Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, Evans or Poort. Given the state of the art with relation to known markers and detecting the markers as indicative of

certain disease which either trigger episodes when exposed to anesthetics, or are poor metabolizers or potentially cause thrombosis are well known. The ordinary artisan would have been motivated to have screened individuals within two days prior to surgery to determine the genetic composition of the individuals to provide individualized diagnosis. Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within any of the known genes for known mutations which are associated with known conditions for the expected benefit of determining whether the patient possessed any mutations which were linked to the known conditions such that the clinician may avoid any adverse reactions to the surgical procedure. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the vast number of teachings, as exemplified by the extremely voluminous Information Disclosure Statement filed, to screen individuals prior to surgery for several genetic markers which are indicative of any number of conditions which are caused by anesthesia or are a result of anesthesia. Hacia teaches that large numbers of probes are placed on arrays for the express benefit of high-throughput mutational analysis with a high degree of accuracy (page 46, col. 2). The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine whether plausible substitutes may be provided to patients which would not cause these conditions to arise. Specifically, detection of RYR1 polymorphisms which are

associated with MH would indicate to the anesthesiologist that drugs which trigger the episodes should be avoided. Moreover, codeine should be administered with care to individuals having certain BchE mutations. Combining more than one screening method to determine the genomic profile of a patient would have provided the anesthesiologist with a more complete picture of the patients genetic make-up. As suggested in many of the articles, individual treatment and screening is ideal for analysis of the genetic make-up of patients.

With respect to the claims drawn to invasive and non-invasive surgery, anesthesia and codine, for example are administered routinely in each of these situations.

With respect to the claims drawn to specific numbers of markers, for example 5 and 10 or more mutations, the skilled artisan would be motivated to screen makers which were well known at the time of the art simultaneously or in tandem for the benefits of providing the most complete amount of information possible. Hacia specifically teaches that arrays to detection mutations of approximately 500 were known in the art at the time the invention was made.

Response to Arguments

The response traverses the rejection. The response filed January 5, 2004 asserts that the cited art fails to establish prima facie obviousness. The claims have been amended to recite testing two or more nucleic acid markers in two or more genes associated with two or more conditions. The response assert that the Examiner has

failed to establish a prima facie case of obviousness. This argument has been thoroughly reviewed, but is not found persuasive. The art teaches

- A method of performing perioperative screening to provide biological information about the patient within 72 hours of the surgery (Miller)
- Once an individual is diagnosed as being susceptible to MH, the anaesthetics which trigger this syndrome can be avoided (Quane). Mutations are taught which are associated with MH.
- Numerous mutations in numerous genes which are associated with toxicity, decreased or increased efficiency, ineffective to various operative drugs (Quane, De Lu, AAS, Poort, Evans, for example)
- Methods using multiple markers provide increased sensitivity over methods employing single markers.
- Arrays for high-throughput and highly accurate mutational analysis which may be used for as many as 500 mutations.

The examiner has set forth a prima facie case which combines all of the teachings and motivations specifically enumerated in the art to obtain the claimed invention as a whole (see rejection above). The express teaching in Quane that "Once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided" provides explicit motivation for testing individuals prior to anesthetics to avoid triggering MH. The ordinary artisan would have been motivated to have avoided triggering MH by performing the genetic testing taught by Quane. Similarly, the ordinary artisan would have been motivated to have not administered SC and mivacurium to

people with BchE deficiency because the art teaches they are potentially toxic. The ordinary artisan would have been motivated to have screened for BCHE deficiency to ensure that they were not providing a potentially toxic drug to their patient. Third, the ordinary artisan would have been motivated to screen for butyrylcholinesterase variants ensure that their patients received the necessary dose of relaxant succinylcholine to achieve the desired state of paralysis. Fourth, since individuals with poor metabolism experience therapeutic failure to codeine, the discovery and identification of polymorphisms in desbrisoquine hydroxylase (Cytochrome P4502D6) saved some lives and may prevent future fatalities or morbidities. The ordinary artisan would be motivated to prevent fatalities and morbidities by testing for polymorphisms in genes. Fifth, given the teachings in the art that "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Further, severe and potentially fatal hematopoietic toxicity that occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches that individualizing drug dosages can improve clinical outcome (page 491, col. 1). The ordinary artisan would be motivated to avoid profound toxicity, reduced efficacy or fatality by testing for polymorphisms. Finally, genetic markers for venous thrombosis in patients have been identified. The ordinary artisan would have been motivated to screen for genetic markers know to be associated with venous thromboembolism to

enable early detection and avoid the serious effects. Overall, the prior art provides a large body of art teaching mutations which are associated with diseases or conditions. The ordinary artisan would have been motivated to have assayed for genetic markers prior to surgery to enable the detection of markers which are negatively associated with surgical conditions so that the conditions may be avoided. Miller teaches that blood samples are taken within 72 hours prior to surgery. The ordinary artisan would have been motivated to have used the blood sample drawn at this point to analyze additional genetic markers such as those taught in the art. Since a blood sample was being taken 72 hours prior to surgery, the ordinary artisan would have been motivated to have avoided an additional blood draw and would have been motivated to have used the blood sample take during this period of time. Minimizing the unneeded discomfort of a patient is of considerable concern by professionals in the medical field.

The examiner has provided sufficient objective evidence clearly provided by skilled artisans. The art further teaches that mutations may be analyzed on arrays, as they are high-throughput and are highly accurate. The ordinary artisan would be motivated to have increased the throughput of the assay and ensure high accuracy by modifying the genetic detection assays with the array based method of Hacia. Therefore, the Examiner has provided a combination of references reflecting the state of the art at the time the invention was made which renders the claims obvious and provides explicit motivation for performing such methods as required by the instant claims.

The response refers to previously submitted references, peer reviews, Declaration and a practice Advisory. Each of these documents were previously considered. As addressed previously, the application for a grant entitled "Perioperative Genomic Profiles" to the Anesthesia Patient Safety Foundation (APSF) and was rejected by a panel of experts because "the state of the art teaches that such methods should not be carried out". Based upon the committees excerpt, the committed states that "the committee's concern and reason for not funding the study rested on a few factors. It is a basic science study without clear clinical value. In the values equation the committee members considered the study might improve the quality but the cost could be very high". While applicants are arguing that the art is not routinely doing perioperative analysis, this is not the standard for obviousness. It is noted that the claim does not require "routine perioperative analysis." There is no requirement that the method be performed routinely. The claim is drawn to a method of perioperatively screening a patient. There are many factors, such as family history, abnormal test results which may motivate a patient or physician to perform a screening method on a particular patient. As provided by the statute of 103,

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

The statute does not provide that cost is a factor in considering non-obviousness. The committee does not appear to be establishing that given the art at the time of filing, that the invention was non-obvious, but the committee rather appears to be indicating

that they do not think that the idea is a cost effective study. The committee has states that "as anesthesia practice has moved toward determining the ratio or quality to cost, this study seems to be going in the opposite direction". This statement is directed to the economical benefits of sampling individuals prior to surgery not the obviousness of studying individuals prior to surgery. Furthermore, the factors considered when determining whether to fund a particular study are completely different than the factors considered in determining that an invention is legally patentable. Grants are often funded because they offer an immediate use, return on value or information that the community may build upon. These are not the criteria which must be met to obtain a patent or to show non-obviousness of the prior art references. The response argues that "this objective evidence of non-obviousness, confuses the fact of non-obviousness ("it would take the issue of patient safety in a new direction"), with the reasons for non-obviousness i.e. cost, confidentiality, ethics. The examiner agrees that the reasons, i.e. cost effectiveness, etc. are immaterial to the finding of non-obviousness, therefore, the reasons given in the grant study are not material to the finding of non-obviousness. The response argues that the Examiner is distracted by cost and economic benefit analysis (page 21 of response). This argument has been thoroughly reviewed, but is not found persuasive because the examiner provide analysis as to why cost is not a consideration in determining obviousness.

The response provides three references directed to the proposition that routine perioperative testing is unnecessary. First, Gregroy teaches that value of routine preoperative screening tests for healthy infants and children has been questioned.

Gregory teaches that "routine preoperative hemoglobin or hematocrit determinations have been recommended in the past, and have been or still are required by law in some jurisdictions. However, there are a few data to support the practice of subjecting every healthy child to a painful fingerprick or venipuncture." (page 184, col 1). While this passage illustrates that individuals may be questioning the need for blood tests prior to surgery many clinicians continue to sample blood and others are required to by law. Therefore, public policy deems it important to perform preoperative blood analysis. Similarly, Kirby teaches that routine laboratory screening tests are not cost-effective and are often inefficient. While routine screening has not yet reached the point of being cost effective and highly efficient, the cited art still provides suggestion that with regard to the RYR1, BchE, prothrombin, etc. genes, testing prior to surgery would be certainly advantageous since mortality and complications may be avoided. While it is clear that many in the medical field do not believe that routine genetic testing provides sufficient valuable information to warrant its cost, this does not imply that the art has not conceived of or thought about the perioperative genetic testing. Once again, the claims are not drawn to routine testing as continually argued by the response. While the art may assert that no perioperative testing is necessary for males who are less than 40, this is not any support that perioperative testing is not necessary for other patients who may be deemed at risk or outside the criteria suggested. The claims are not limited to males less than 40 years of age who are undergoing surgery with minimal expected blood loss.

The response cites Hopkins to support, "the complexity of the molecular genetics of MH precludes DNA-based diagnosis at present. Thus, a modern analysis of the molecular genetics of MH concludes that DNA-based testing for MH is precluded and not desirable". The claims are drawn to detecting two or more genetic markers to generate a genomic profile useful in selecting perioperative course of action. The claims are not drawn to diagnosing MH. The claims are drawn to screening a patient perioperatively to determine a risk for complications; a method for selecting conditions for a surgical procedure; a method of screening a patient perioperatively to determine a risk for complications during said surgical procedure.

With respect to what the ordinary artisan would have recognized or appreciated, Quane teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided. Quane is at least an ordinary artisan if not a skilled artisan. Quane clearly recognized the benefit of testing an individual prior to surgery to avoid triggering MH. Thus, the skilled artisan did recognize the benefit of screening individuals prior to surgery to avoid known conditions triggered by particular mutations or markers in genes.

The second declaration of Kirk Hogan, filed July 8, 2002, has been thoroughly considered, but found not persuasive. The declaration asserts that the state of the art has not tested subjects for genetic markers during the perioperative period. The declaration reviews a Practice Advisory for Preanesthesia Evaluation: A report by the American Society of Anesthesiologist Task Force on Preanesthesia Evaluation". The declaration asserts that no perioperative genetic testing of any kind is advocated,

discussed or mentioned. This silence with respect to genetic testing does not mean that the testing would be unobvious. While the article may not specifically consider genotypes for preanesthesia evaluation does not provide evidence that the combination of the cited references do not provide the legal standard for obviousness. The teachings of the article are not directed to the non-obviousness of the invention. The examiner has set forth objective evidence in the form of references to establish a prima facie case of obviousness. The response has selected certain passages from the evaluation which do not appear to represent the full teachings of the reference. The Practive Advisory for preanesthesia evaluation states that the study is intended to assist decision-making in areas of patient care, but not intended as guideline, standards or absolute requirements. The evaluation may be "adopted, modified or rejected according to clinical needs and constraints (abstract). Moreover, preoperative tests may be indicated for various purposes including discovery or identification of a disease or disorder that may affect perioperative anesthetic care. It is noted that MH as taught by Quane is a disorder which will affect preoperative anesthetic care. Therefore, the reference does not appear to support the assertion that preoperative care precludes the testing of genetic markers. "The Task Force agrees that preoperative tests may be ordered, required, or performed on a selective basis for purposes of guiding or optimizing perioperative management. The indications for such testing should be documented and based on information obtained from medical records, patient interview, physical examination and type and invasiveness of the planned procedure" (page 490, col 1-2). Moreover, the Task force "believes that there is insufficient evidence to identify

explicit decision parameters or rules for ordering preoperative tests on the basis of specific clinical characteristics" (page 490, col 1-2). Note 4, states that "selective preoperative tests (i.e., tests ordered after consideration of specific information obtained from sources such as medical records, patient interview, physical examination and the type of invasiveness of the planned procedure and anesthesia) may assist the anesthesiologist in making decisions about the process of preoperative assessment and management (page 493, col. 1). Therefore, based upon the teachings of the reference as a whole, the reference does not state that preoperative tests should not be done.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning (page 13), it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The examiner's position is not based upon improper hindsight. The art clearly provides motivation. Quane, for example teaches that "once an individual is diagnosed as being susceptible to MH, the anaesthetics which trigger this syndrome can be avoided." This explicit teaching to avoid anaesthetics which trigger MH is motivation to avoid administering anesthetics to patients with particular mutations. Therefore, the combination of references is permissible.

Applicant then argues this is an "obvious to try" situation (page 14). The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e. , a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art that polymorphisms are known to be associated with complications due to anesthesia as taught by Quane. There is further evidence as shown by DeLu, Poort, AAS, Evans, for example. This sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

> "In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g ., In re Geiger , 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91

(Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987); In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art directly points to the use of particular markers for avoiding particular conditions, diseases or negative reactions. This is also not a situation where only general guidance was given. The prior art provides specific guidance directing the use of particular mutations, particular diseases, for example. The response appears to also argue that there is no reasonable expectation of succession in using Hoon. This argument has been thoroughly reviewed, but is not found persuasive for the reasons above. Multiplexing or arraying more than one mutation was well known in the art at the time the invention was made (see Hoon and Hacia). The ordinary artisan would have been motivated to have selected two or more markers taught in the art to be associated with negative perioperative aspects since Hoon teaches two markers is more significant than a single marker. Further, Hacia provides a clear means for assaying for more than one marker, i.e. an array. The ordinary artisan would have a reasonable expectation of success of assaying for more than one marker on an array since the prior art performs as many as 500 markers on a single array.

The response further argues that the Hoon patent is directed to melanoma or breast cancer cells such that they are markers which are tissue and cancer specific.

This argument has been thoroughly reviewed, but is not found persuasive because the general teaching of Hoon provides that multiple markers from multiple genes was more effective than a single marker alone. There is a reasonable expectation that the more markers used, the greater the significance. The ordinary artisan would reasonably expect that using multiple markers, such as RYR1, BCHE, CYP2D6, for example, would similarly yield significantly increased results as compared to the markers individually. The teachings of Hoon cover the idea of combining alleles for improved detection sensitivity and the teachings are not limited to the subject matter granted protection in the claims. To argue that the only teachings which may be used in a patent are the claims, would render the specification's teachings meaningless for art purposes.

The response briefly addresses Quane. The response asserts that Quane fails to teach that samples are tested in the perioperative period. This argument has been thoroughly reviewed, but is not found persuasive because Miller is used in the combination to show obviousness. It is noted that this is a rejection under 103 and not 102 anticipation. The applicant appears to argue that obviousness is anticipation. As provided in 706.02, "in a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. The modification must be one which would have been obvious to one of ordinary skill in the art at the time the invention was made." The response argues that Quane does not teach or suggest that anyone should be screened prior to surgery. This argument has been thoroughly reviewed, but is not found persuasive because the claim is not directed to patients who "are believed to be healthy going into the test." The claim is drawn to a patient.

Further, Quane teaches that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided." The response further argues that the Quane is only direct to a single gene and condition (page 29). This argument has been thoroughly reviewed, but is not found persuasive because the rejection also contains numerous other references which contain additional mutations, genes and conditions to facilitate the obvious type rejection.

Thus, for the reasons above and those already of record, the rejection is maintained.

Conclusion

6. **No claims allowable.**

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Brandt et al (Human Molecular Genetics, Vol. 8, No. 11, pages 2055-2062, 1999) teaches that 21 RYR1 mutations have been identified which account for more than 50 of the families with susceptibility to MH. Brandt teaches that the genetic testing may be used to determine whether individuals are likely to have MH.

B) Ciccone et al (herein referred to as Ciccone) teaches that "In anaesthesia, our preoperative assessment includes prescribed medications and allergies to drugs. We also consider factors, either directly or indirectly, which may influence responses to drugs, such as age, genetic history, metabolic phenotype,..." (page 255-256).

C) Monnier et al (herein referred to as Monnier) teaches a novel mutation in CACLN1A3 which segregate perfectly with the MHS phenotype in a French family. The substitution of an Arg-His at residue 1086 results in the transition of A for G3333.

D) Jensen et al (Acta Anaesthesiologica Scandnavica, Vol 39, page 150-156) teaches that patients with abnormal BchE often have prolonged apnoea following succinylcholine. Jensen teaches that on should not try to treat the block, but rather keep the patient anaesthetized and ventilated till the usually clinical criteria for full recovery are present. Further, when a clinician is faced with a patient with an apparent abnormal response to succinylcholine, the use of a nerve stimulator is urged.

E) Masterson et al (Br. J. of Anaesthesia, Vol 77, No. 5, page 569-571, 1996) teaches that patients which are likely to mount excessive cytokine responses after surgery may be tested. "Such tests may help anaesthetists to predict outcome or the need for postoperative intensive care. They may also allow us to select the most appropriate anaesthetic, in terms of its ability to modulate cytokine activity, for each patient.

F) Caplan teaches numerous costs of adverse outcomes for anesthesia-related deaths. Among these costs is not only the economic costs, but also non-economic costs.

G) Larson et al (herein referred to as Larson) teaches the preoperative testing for a T to C transition in the codon for amino acid 85 of the beta globin gene. The individual was tested for an unstable Hb variant resulting in congenital hemolytic anemia which has an increased affinity for oxygen. Larson teaches that chronic hemolysis may

result in cholelithiasis requiring cholecysterctomy. Perioperative management of this congenital hemoglobinopathy by partial-echange erythrocytapheresis to prevent introperative tissue hypoxia during general anesthesia and cholecystectomy. Lason describes the "perioperative management of a patient, with the unstable, high-oxygen-affinity Hb, HbBryn Mawr, who was deemed at risk for significant tissue hypoxia during general anesthesia and surgery".

H) Hecht et al (Anesth. Analg, Vol. 84, pg. 461-464, 1997) teaches a G1583A mutation in CACNL1A3 which is associated with HypoPP. Hecht also teaches that HypoPP has been identified as a disorder that can predispose a patient to the syndrome of MH which the risk of triggering skeletal muscle contraction and rhabdomyolysis, together with earlier reports of flaccid paralysis aggravated by surgery and general anesthesia, appear to favor regional anesthesia in this population whenever feasible (abstract). Hecht also teaches that MH susceptibility associated with HypoPP and of hypokalemia elicited by regional anesthesia suggests that hybrid anesthetic techniques be avoided (pg. 462, col. 2).

I) Korte et al (Clin. Chem. Lab. Med, Vol. 36, No. 4, pg. 235-240, 1998) teaches to establish a possible "perioperative reference range" for thrombin generation prothrombin fragment F1+2 and fibrin degradation markers were measured (abstract). Korte also teaches that preoperative determination of molecular markers would be helpful in identifying a group of patients at high risk for intraoperative disorder of hemostasis by exclusion of low risk patients (abstract). As seen in Table 2 and Table 3, the results of the detection assay for the two genetic markers were observed (pg. 237).

J) Brandt et al (Hum. Mol. Genetics, Vol 8, No. 11, pg 2055-2062, 1999) teaches screening of approximately 105 MH families for mutations. Despite the extensive number of known mutations in RYR1, "interpretation must be performed with care because lack of the particular mutation segregating in the family does not exclude absence of further independent unknown mutations. Additionally, genetic screening is not yet suitable for routine diagnostics due to the low incidence of each mutation and the vastness of the gene" (pg 2058, col 2).

K) De Stefano et al (New England J. Med, Vol 341, pg 801-806, 1999) teaches screening for two point mutations, one in F 5 Leiden and one in the prothrombin gene which are the most common causes of inherited thrombophilia. Thus, carriers of both of these mutations have an increased risk of recurrent deep venous thrombosis after a first episode and are candidates for lifelong anticoagulation.

1. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

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J. Goldberg

Jeanine Goldberg
Patent Examiner
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